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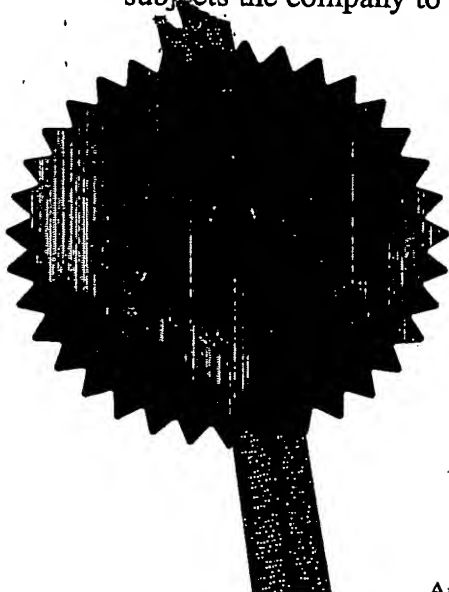
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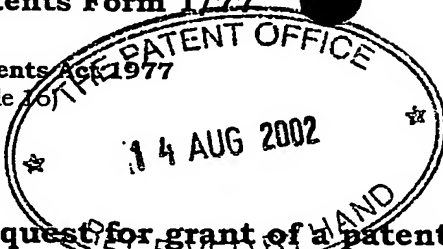
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15AUG 1977 5741300-2 D00524  
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**1/77**

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1.	Your reference	4-32616P1		
2.	Patent application number (The Patent Office will fill in this part)	0218996.7		
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND		
	Patent ADP number (if you know it) If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND		7125487005
4.	Title of invention	Organic compounds		
5.	Name of your agent (if you have one)  "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		Novartis Pharmaceutical UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number (if you know it)	1800001		
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year )
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)	
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:			
	a) any applicant named in part 3 is not an inventor, or			
	b) there is an inventor who is not named as an applicant, or			
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## Patents Form 1/77

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Description 8

Claim(s) 1

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*) ONE

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
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11. I/We request the grant of a patent on the basis of this application

Signature

Date

B.A. Yorke & Co.

B.A. Yorke & Co.

14 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham  
020 8560 5847

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Organic compounds

The present invention relates to topical pharmaceutical compositions comprising an ascomycin or a compound of the FK 506 class for the treatment of skin disorders, particularly in form of a topical solution.

- 5 Ascomycins or derivatives thereof, e.g. a compound of the FK 506 class. FK506 is a known macrolide antibiotic that is produced by Streptomyces tsukubaensis No 9993. It is also a potent immunosuppressant. The structure of FK506 is given in the appendix to the Merck Index, 11th Edition as item A5. Methods of preparing FK506 are described in EP 184162.

- 10 A large number of derivatives, antagonists, agonists and analogues of FK506, which retain the basic structure and at least one of the biological properties (for example immunological properties) of FK506, are now known. These compounds are described in a large number of publications, for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385, WO 93/5059 and the like. Ascomycins and derivatives thereof, including  
15 FK506, are referred to hereinafter as "ascomycins".

Ascomycins and derivatives thereof such as macrolactam compounds of the FK506 class are known to be extremely useful in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses.

- 20 The condition of the skin to be treated may vary e.g. with kind and grade of disease; e.g. the skin may be dry or fatty skin. Furthermore, the skin to be treated may be haired. Thus, there is a need for a pharmaceutical composition that may be applied to the skin substantially independent of the condition of the skin.

- 25 Applicants have now surprisingly found that an ascomycin as active agent can be formulated into a pharmaceutical composition, e.g. in form of a topical solution, for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses, e.g. independent of the condition of the skin. These pharmaceutical compositions, hereinafter termed compositions of the invention, are effective independent of the condition of the skin, well tolerated on the skin, stable and exert particularly

interesting absorption and skin penetration properties.

Thus, in one aspect this invention provides a pharmaceutical composition of an ascomycin, e.g. in form of a topical solution. In a preferred embodiment the present invention provides a pharmaceutical composition of an ascomycin, e.g. in form of a topical solution, which composition comprises a carrier vehicle comprising i) a lower alkanol and/or alkanediol and ii) a fatty alcohol.

Preferred ascomycins for use in the present invention include FK506; 33-epi-chloro-33-desoxy-ascomycin as disclosed in Example 66a in EP 427680 (hereinafter referred to as Compound A); {[1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16, 20-trihydroxy-4-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-aza-tricyclo[18.6.1.0(1,22)]heptacos-10-ene-2,8,21,27-tetraone as disclosed in Examples 6d and 71 in EP 569 337 (hereinafter referred to as Compound B); and {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.0(4,9)]octacos-5,18-diene-2,3,10,16-tetraone, also known as 5,6-dehydro-ascomycin as disclosed in Example 8 in EP 626 385 (hereinafter referred to as Compound C).

The active agent may be e.g. present in the compositions of this invention in an amount of from e.g. 0.05 to 10% by weight, e.g. from 0.1 to 5% by weight, e.g. from 1 to 3% by weight based on the total weight of the composition.

Examples of lower alkanols may comprise a straight or branched chain saturated, e.g. C<sub>3</sub> to C<sub>8</sub>, alkanol, e.g. isopropanol. Preferably, the compositions of the present invention are substantially free of ethanol.

Examples of lower alkanediols may comprise, e.g. C<sub>1</sub> to C<sub>8</sub> alkanediols, e.g. propylene glycol (1,2-propanediol), butylene glycol, 2-ethyl-1,3-hexanediol, hexylene glycol (2-methyl-2,4-pentanediol) and the like. Preferred alkanediols are propylene glycol and hexylene glycol.

Examples of a fatty alcohol may comprise a mono- or polyunsaturated fatty alcohol, for example a C<sub>12</sub> to C<sub>24</sub>, e.g. C<sub>16</sub> to C<sub>18</sub>, mono- or polyunsaturated fatty alcohol, preferably oleyl alcohol or elaidic alcohol, although oleyl alcohol is particularly preferred.

The lower alkanol and/or alkanediol may preferably be present in the compositions of the invention in an amount of about 10 to about 90% w/w, more preferably from e.g. 40 to 90% w/w.

5 The fatty alcohol may be present in the compositions of this invention in an amount of from about 10 to about 60% w/w, more preferably 50 to 60% in total.

The compositions of the invention may further comprise iii) an alkane carboxylic alkyl ester, e.g. a  $C_{12}$  to  $C_{24}$ , preferably  $C_{14}$  to  $C_{16}$ , carboxylic acid ester, e.g. isopropyl myristate, ethyl myristate, isopropyl palmitate and the like; and/or an alkane dicarboxylic ester, e.g. a  $C_2$  to  $C_{10}$  alkane dicarboxylic ester, e.g. diisopropyl adipate, diethyl adipate and the like, in amount of from e.g. 5  
10 to 50%, preferably from e.g. 10 to 50% ww.

The compositions of the invention may further comprise iv) an additional hydrophilic component, a "hydrophilic co-component". This hydrophilic co-component may include a pharmaceutically acceptable ether diol, e.g. dipropylene glycol, diethylene glycol and the like; a diether alcohol, e.g. diethyleneglycol mono ethyl ether and the like; a di- or partial ether of a  
15 low molecular weight mono- or polyoxyalkanediol, e.g. Glycofuro, diethylene glycol monoethyl ether (Transcutol); triethyl citrate; N-methylpyrrolidone, dimethylisosorbide; or propylene carbonate; preferably dimethylisosorbide. These components may consist of one component or a mixture of components and may be present in amount of from e.g. 5 to 50%, preferably from e.g. 10 to 50% w/w.

20 Preferably the ascomycin and the alkanol and/or alkanediol, are present in a weight ratio of 0.05 to 10 : 10 to 60, more preferably in a weight ratio of 0.5 to 10 : 50 to 60, even more preferably in a weight ratio of 1 to 3 : 50 to 60.

Preferably the ascomycin and the fatty alcohol are present in a weight ratio of 0.05 to 10 : 5 to 90, more preferably in a weight ratio of 0.5 to 10 : 5 to 50, even more preferably in a weight  
25 ratio of 1 to 3 : 10 to 20.

Preferably, the compositions of the present invention are non-greasy formulations. Absence of greasiness and low residue upon application may lead to an increased convenience especially on haired skin. Preferably, the compositions are substantially free of water, i.e. they do not contain any added water.

30 The components of the compositions of the invention may be described in Fiedler, H. P.

"Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), the contents of which are hereby incorporated by reference.

The compositions of the invention may also include anti-oxidants such as such as butyl-  
5 hydroxytoluene, ascorbyl palmitate, sodium pyrosulfite, butyl hydroxy anisole, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate and tocopherol, as appropriate. The anti-oxidants serve to prevent bacterial growth, and are preferably present in an amount of about 0.01 to about 2.5% w/w.

Due to easier application a thickened solution, e.g. a semi-solid solution or a fluid-gel or a  
10 transparent gel, may be desirable. This can be achieved by adding conventional viscosity enhancing components or consistency agents to the compositions described above. Suitable viscosity enhancing components include, e.g.

- polyacrylic acid, as known under the names carboxypolymethylen, or carboxyvinylpolymer, or carbomer, or Carbopol®
- 15 - cellulose derivatives including e.g. ethyl, propyl-, methyl- and hydroxypropylmethyl-celluloses,
- colloidal silica, e.g. Aerosil®,
- polyvinyl alcohol,
- polyvinyl pyrrolidone, and
- 20 - polymethylacrylate resins, e.g. Eudispert.

Suitable consistency agents include solid alcohols, having e.g. a C<sub>12</sub> to C<sub>24</sub> chain, e.g. cetyl alcohol and/or stearyl alcohol. Cetyl alcohol and stearyl alcohol may be commercially available e.g. under the trade names Lorol® C16 and Lorol® C18, respectively, from Henkel, Germany. Upon application of the compositions of the present invention on the skin, the lower  
25 alkanols may evaporate to yield a supersaturated system which enhances penetration.

The compositions of the invention are useful in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases. Examples of immunologically-mediated diseases include alopecia areata, psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoic

dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, and lupus erythematosus. Examples of skin diseases include dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, acne, autoimmune diseases such as  
5 chronic rheumatoid arthritis, scleroderma and the like.

In another aspect, the present invention provides a composition as defined above for the use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

In another aspect the present invention provides a method for treating inflammatory and  
10 hyperproliferative skin diseases or of cutaneous manifestations of immunologically-mediated diseases comprising administering a composition of the invention to the skin of a patient in need thereof.

In yet another aspect, the invention provides the use of a composition of the invention in the preparation of a medicament for the treatment of inflammatory and hyperproliferative skin  
15 diseases and of cutaneous manifestations of immunologically-mediated diseases.

In yet another aspect the present invention provides the use of a carrier vehicle as defined above to enhance penetration of an ascomycin into human skin. The compositions of the present invention may be e.g. in form of a topical spray solution.

The compositions of the invention may be prepared in a conventional manner by working up  
20 the components into a pharmaceutical composition.

For example, the composition of the invention may be obtained by dissolving an ascomycin in a pharmcologically acceptable alkanol, e.g. a lower alkanol, alkanediol and/or a fatty alcohol. Other components, e.g. alkane carboxylic alkyl esters and/or alkane dicarboxylic esters and/or hydrophilic co-components, excipients, etc. may be added at the appropriate time to the  
25 appropriate phase as is conventional.

The utility of the compositions according to the invention can be observed in standard clinical tests such as the test set out below using a concentration of 0.005 to 10% w/w (preferably 0.1



to 3% w/w) of the active agent. The utility can also be observed using standard animals models as described in EP 315978.

A representative clinical trial is carried out as follows:

- A randomised double-blind, vehicle-controlled within-patient study comparing the composition of the invention at a dose of 0.1 to 3% by weight (based on the total weight of the composition) active agent on the diseased skin area, e.g. 200 cm<sup>2</sup>, corresponding to about 0.5 to 50 mg/cm<sup>2</sup>, preferably 1 to 10 mg/cm<sup>2</sup> of composition, and Placebo on the diseased skin area as positive control is performed in patients suffering from inflammatory and hyperproliferative skin diseases or of cutaneous manifestations of immunologically-mediated diseases.
- 10 The patients are treated with the composition twice daily for six months. The therapeutic effect is evaluated and the time to partial clearance is used for efficacy. Local tolerability of study medications and routine safety parameters, including haematology and clinical chemistry, are recorded.

- The exact amount of the compound and the composition of the invention to be administered depends on various factors, for example the desired duration of treatment and the rate of release of the active agent. Satisfactory results are obtained in larger mammals, for example humans, with the local application over the area to be treated of a 0.05 to 10% w/w, preferably 0.1 to 3%, concentration of the active agent once or several times a day (for example 2 to 5 times a day). In general the composition may be applied to areas of skin as small as 1 cm<sup>2</sup> to as large as 0.5 m<sup>2</sup>, preferably the composition will be applied to the head area in the treatment of inflammatory and hyperproliferative skin diseases or of cutaneous manifestations of immunologically-mediated diseases. Suitable skin loadings of the active agent fall within the range of 0.005 mg/cm<sup>2</sup> to 1 mg/cm<sup>2</sup>.
- 15  
20

- The compositions of the invention are found to be effective independent of the condition of the skin and are well tolerated on skin. The compositions of the present invention may be easily applied to large areas of skin using a conventional applicator, e.g. brush, cotton pad, filament, topical spray or roller ball applicator, and are thus very convenient. The compositions of the present invention are especially suitable for application on haired skin areas. Good skin penetration and permeation rates may be achieved using the compositions of this invention.
- 25

The compositions of this invention have the advantage of few components, are straightforward to prepare and are well-tolerated on human skin.

All percentages referred to herein are weight/weight except where otherwise indicated.

Following is a description by way of example only of compositions of the invention.

## 5 EXAMPLES

The term stable, as used in the following Examples, will be understood to mean that no separation of components is observed of the respective composition when stored at room temperature for a period of at least 3 months or longer and that there is no decomposition of active agent.

1.0 Chemical analysis of the active agent is undertaken using reverse phase HPLC with UV detection;  $\lambda = 210$  nm. Quantification limit is 0.1% by weight.

### Examples 1 to 4

The following compositions were prepared.

	Ex.1	Ex.2	Ex.3	Ex.4
compound A	1%	1%	8%	1%
isopropanol	49%	49%	42%	47%
oleyl alcohol	10%	10%	10%	10%
propylene glycol	40%	-	-	-
isopropyl myristate	-	40%	-	40%
dimethylisosorbide	-	-	40%	-
hydroxypropyl cellulose	-	-	-	2%

The compositions of Examples 1 to 4 are stable.

Examples 5 to 12

The following compositions were prepared.

	Ex.5	Ex.6	Ex.7	Ex.8	Ex.9	Ex.10	Ex.11	Ex.12
compound A	1%	1%	1%	1%	1%	1%	1%	1%
isopropanol	89%	39%	39%	39%	39%	39%	39%	39%
oleyl alcohol	10%	10%	10%	10%	10%	10%	10%	10%
hexylene glycol	-	-	-	40%	1%	1%	1%	1%
isopropyl myristate	-	-	-	-	40%	-	-	-
isopropyl palmitate	-	-	-	-	-	50%	-	-
dimethyl isosorbide	-	50%	-	-	-	-	50%	-
diisopropyl adipate	-	-	50%	-	-	-	-	50%

The compositions of Examples 5 to 12 are stable.

Examples 13 to 20

5 The following compositions were prepared.

	Ex.13	Ex.14	Ex.15	Ex.16	Ex.17	Ex.18	Ex.19	Ex.20
compound A	0.2%	2%	2%	0.5%	0.5%	0.5%	5.0%	2%
oleyl alcohol	10%	10%	10%	10%	10%	10%	10%	10%
propylene glycol	89.8%	38%	38%	-	-	-	-	-
hexylene glycol	-	-	-	89.5%	39.5%	39.5%	35%	38%
isopropyl myristate	-	-	-	-	50%	-	-	-
isopropyl palmitate	-	-	-	-	-	50%	-	-
dimethyl isosorbide	-	50%	-	-	-	-	50%	-
diisopropyl adipate	-	-	50%	-	-	-	-	50%

The compositions of Examples 13 to 20 are stable.

**CLAIMS:**

1. A pharmaceutical composition of an ascomycin which composition comprises a carrier vehicle comprising i) a lower alkanol and/or alkanediol and ii) a fatty alcohol and optionally iii) an alkane carboxylic alkyl ester and/or an alkane dicarboxylic ester and/or optionally iv) a hydrophilic co-component.  
5
2. A composition according to claim 1 wherein the ascomycin is present in an amount of 1 to 3% by weight of the composition.
3. A composition according to claim 1 or 2 wherein the ascomycin is 33-epi-chloro-33-desoxy-ascomycin.  
10
4. A composition according to any preceding claim which is substantially free of ethanol.
5. Use of the carrier vehicle as claimed in any preceding claim to solubilize and/or enhance penetration of an ascomycin into human skin.
6. A pharmaceutical composition substantially as hereinbefore described with reference to the Examples.  
15